When Is a Clinical Growth Study Needed?

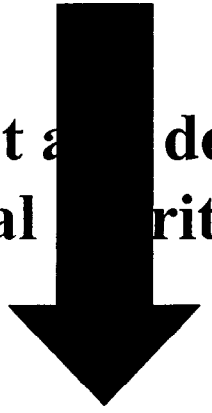
Industry's Current Analysis and Documentation Process

José M. Saavedra, M.D.
Medical Director
Nutrition Division, Nestlé USA

ATTACHMENT J

Current Process and History: Nutritional Adequacy

Industry considers a change to current formula



Assessment a documentation of potential ritional impact

Industry notifies FDA of all major and minor changes that may impact their nutritional adequacy

Current Evaluation and Assessment of Changes to Infant Formula

…to determine need for clinical trials to confirm that an infant formula supports normal growth (nutritional adequacy)

We engage in a process…

Decision Criteria for Clinical Trials

- Clinical trials should be done:
  - If it can reasonably be predicted that change will have an impact on growth
- Clinical trials should not be done
  - If redundant, unnecessary or unethical
- Decision :
  - Based on specific reasonable and conservative assessment and evaluation of the change
- Industry decisions are always subject to FDA review

The Regulatory Safety Net: Industry Accountability & FDA Notification

Minor Change	**Major Change/New Formula**
Notify Prior to 1st Processing	90-day Pre-market Notification
Supported by well accepted scientific rationale and meeting all IFA/regulatory requirements--no clinical trial necessary	Nature of change and supporting scientific rationale determine submission requirements. Some testing necessary - may or may not include clinical.

Only if <u>neither</u> applies is FDA notification <u>not</u> required

Decision Tree Chart for Documentation of Nutritional Adequacy of a New or Changed Infant Formula

Minor Change *

Notify Prior to 1st Processing

Supported by well accepted scientific rationale and meeting all IFA/regulatory requirements--no clinical trial necessary

Major Change/New Formula**

90-day Pre-market Notification

Nature of change and supporting scientific rationale determine submission requirements. Some testing necessary - may or may not include clinical.

Potentially Significant Packaging Change

Possible Issues:
- nutrient stability
- product contamination

Documentation:
- consider most appropriate means to address issue, clinical support *unlikely* to be necessary

Potentially Significant Process Change

Possible Issues:
- nutrient homogeneity
- nutrient stability
- product contamination

Documentation:
- consider most appropriate means to address issue, clinical support *unlikely* to be necessary

Potentially Significant Formulation Change

Possible Issues:
- non-comparable nutrition
- nutrient stability

Documentation:
- depending on potential nutritional impact and availability of other evidence, clinical support *may* be needed

Potentially Significant New Ingredient or Source

Must have GRAS or Approved Food Additive status

Possible Issues:
- non-comparable nutrition
- nutrient stability
- product adulteration

When supported by well accepted scientific rationale and/or experience in this or similar formulation

Documentation:
- depending on potential nutritional impact and availability of other evidence, clinical support *may* be needed

When not supported by well accepted scientific rationale and/or experience in this or similar formulation

Documentation:
- depending on potential nutritional impact and availability of other evidence, clinical support *likely* to be needed

* Where experience or theory would predict no possible significant adverse impact on nutrient levels or nutrient availability

** Where manufacturer's experience or theory would predict possible significant adverse impact on levels of nutrients or bioavailability of nutrients, or any change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer

What is a Major Change ?

- A wholly new formula, by a manufacturer who has not made infant formula in the US

or

- A change in a current formula where manufacturer's experience or theory would predict possible significant adverse impact on levels of nutrients or bioavailability of nutrients

or

- A change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by a current US manufacturer

Documentation for Major Changes

- Convincing documentation required to demonstrate that the formula will support normal growth.
- The nature of change and supporting scientific rationale determine submission requirements.
- Supportive data are always necessary – but may or may not include a clinical trial.

Assessment and Evaluation of Changes
Sources of Documentation

- Published guidelines:
  - AAP/CON
  - NAS
  - ADA
  - ASPEN
  - NASPGHN

Assessment and Evaluation of Changes

Sources of Documentation

- Published literature
  - medical
  - food science
  - nutrition
  - chemistry
  - microbiology

Assessment and Evaluation of Changes

Sources of Documentation

Previous experience

- Product
  - Processing, Ingredient, Batching, Packaging, Shelf life
- Testing
  - Pre clinical: *In vivo* and *in vitro* testing
  - Clinical

Assessment and Evaluation of Changes

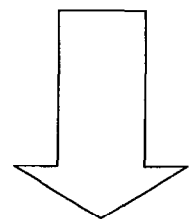
Sources of Documentation

- Internal medical scientific assessment
- Independent expert review

Assessment and Evaluation of Changes

Sources of Documentation

If after looking at entire process, and based on all available sources of documentation there is any remaining question as to nutritional adequacy….



Clinical Trials

Last Ten Years
Approximately

- 100 Minor Change Submissions
- 150 Major Change Submissions
- 50 Growth Studies in 6,000 infants

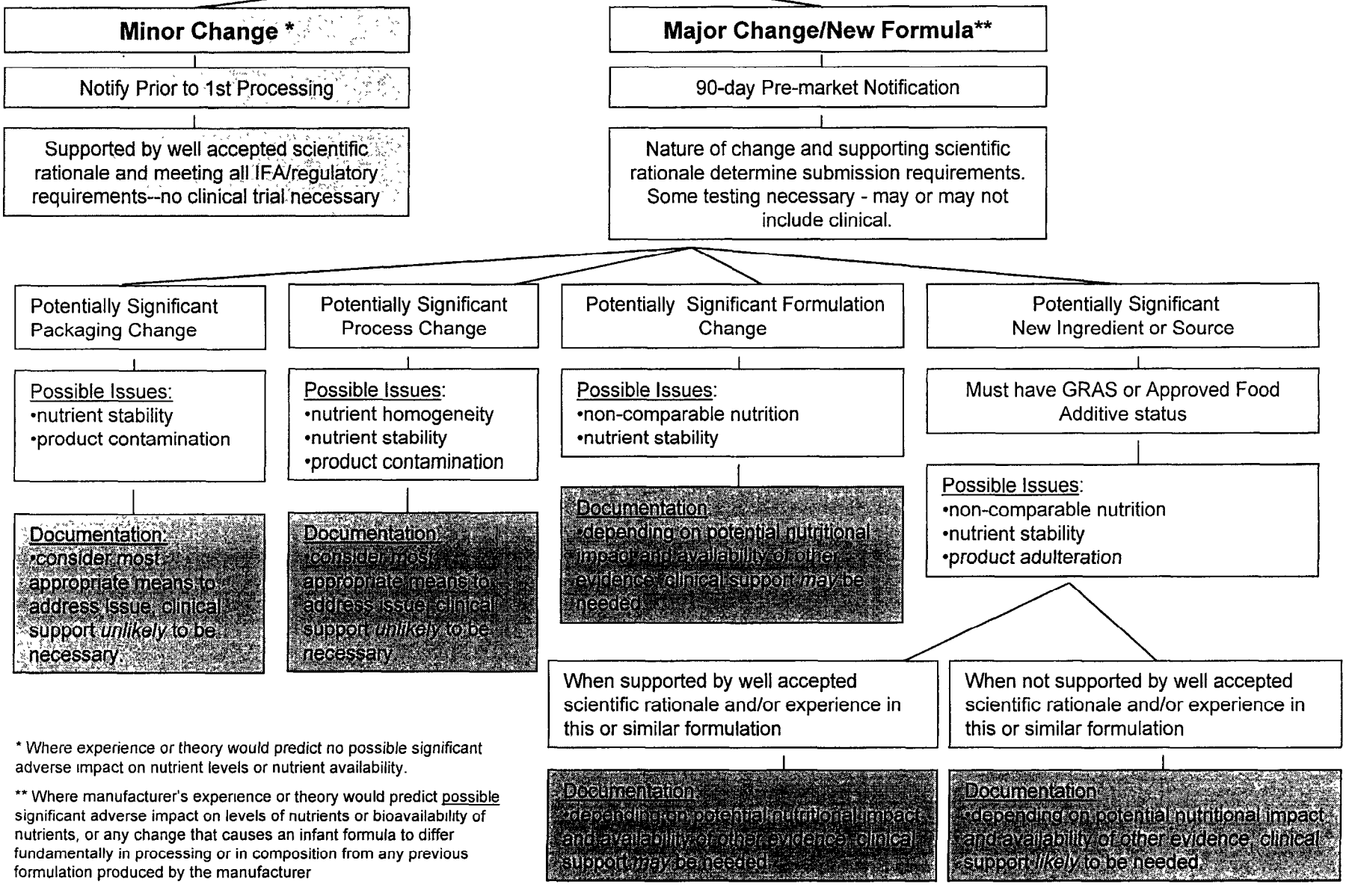
Infant Formula Today

"In developed countries at the end of the century, the mortality, health, growth and development of formula fed infants are largely indistinguishable from those of infants who are breast-fed."

Current Process and History: Nutritional Adequacy

Since IF Act (1980) not a single nutrition based problem has resulted from formulation changes in infant formula.

Decision Tree Chart for Documentation of Nutritional Adequacy of a New or Changed Infant Formula



* Where experience or theory would predict no possible significant adverse impact on nutrient levels or nutrient availability.

** Where manufacturer's experience or theory would predict possible significant adverse impact on levels of nutrients or bioavailability of nutrients, or any change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer